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On BIOLOGICAL EFFECTS OF PROLONGED EXPOSURE OF ANIMALS TO UNUSUAL GASEOUS ENVIRONMENTS

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SUB TITLE: Lung weights of rats exposed to hyperoxic gas mixtures in which He or no inert gas replaces N_2.

Rats generally survive indefintely in environments in which the P_{O_2} is less than 600 Torr, usually with little evidence of O_2 toxicity except for depressed food intake and decreased growth. At P_{O_2} greater than 600 Torr, respiratory symptoms of varying severity, including atelectasis, congestion and edema, often leading to death, are expected generally within a few days. The purpose of this study was to see if the lower, nonlethal but still hyperoxic ranges had any measurable effect on the lungs, and whether the presence, absence or type of inert gas (i.e., N_2 or He) associated with the O_2 exerted any influence on the O_2 effect.

Approximately 250 g male Sprague-Dawley (Holtzman) rats were exposed to the hyperoxic gas mixtures indicated in Table 1, utilizing sealed recirculating isolators for environmental control. The 100 O_2 exposure was carried out with the isolator held within an altitude chamber set at 570 torr; 570 torr of 100% O_2 was calculated to provide an alveolar P_{O_2} approximately equivalent to 74% O_2 at the 750 mmHg which was taken as average ground level pressure at Columbus (i.e., P_{O_2} = 555 torr). Six to ten rats were sacrificed after 10 and 20 days of exposure. Lungs were removed and weighed fresh, then dried at 105°C for 24 hrs. and reweighed. Two control groups were run: one fed ad lib, the other restricted-fed in an effort to stimulate the lower intake found with the O_2 treatments.

The body weight measurements indicate that all O_2 treatment depressed growth, with the 100% O_2 group showing essentially no growth at all above its starting weight at either 10 or 20 days. The N_2 and He groups showed a little growth during the first 10 days but nothing further during the second 10 days. The weight of the restricted-fed group was close to that of the He and N_2 groups.

At ten days it is evident that both wet and dry lung weights (as a proportion of body weight) are greater in all the O_2 treatments than in either control group, indicating some sort of lung damage. The two control groups do not differ between themselves suggesting that simple body weight changes resulting from different food intakes does not alter the ratio of either wet or dry lung weight to body weight. Since the % increase in lung weight over that of the restricted-fed controls is the same for the wet and dry measurements (Table 1), it must be concluded that the ten-day O_2 effect on the lungs is due essentially to tissue proliferation rather than edema.

At 20 days, the same relative lung weight picture is seen but with some modifications. The two controls again do not differ in lung weight/body weight ratio although their body weights are considerably more divergent than at 10 days. This further supports the view that lung

Table 1 - Lung and Body Weight Changes in Rats Exposed for 10-20 Days to 74% O_2 at One Atmosphere, with and without Inert Gas Diluents

	NUMBER	AVERAGE ± STANDARD ERROR						
		TEN DAYS			NUMBER	TWENTY DAYS		
		BODY WEIGHT (g)	Lung Wt/Body Wt. (g/100 g)			BODY WEIGHT (g)	Lung Wt/Body Wt. (g/100 g)	
			WET	DRY			WET	DRY
1) 100% O_2 (570 torr) (as % of restricted-fed)	10	255 ± 5.6 (92)	0.62 ± 0.03 (122)	0.14 ± 0.01 (118)	10	254 ± 0.95 (93)	0.79 ± 0.11 (134)	0.16 ± 0.02 (139)
2) 74% O_2-26% N_2 (1 Atm) (as % of restricted-fed)	10	275 ± 6.6 (99)	0.64 ± 0.02 (126)	0.15 ± 0.01 (128)	10	267 ± 7.2 (98)	0.87 ± 0.17 (147)	0.19 ± 0.02 (167)
3) 74% O_2-26% He (1 Atm) (as % of restricted-fed)	10	279 ± 49 (101 L)	0.63 ± 0.01 (124)	0.15 ± 0.01 (128)	9	289 ± 6.0 (106)	0.62 ± 0.02 (104)	0.12 ± 0.01 (111)
4) Room air controls, restricted-fed	10	277 ± 2.6	0.51 ± 0.03	0.12 ± 0.01	10	272 ± 5.8	0.58 ± 0.05	0.11 ± 0.01
5) Room air controls, ad lib-fed	10	305 ± 3.1	0.53 ± 0.01	0.12 ± 0.01	6	336 ± 9.4	0.57 ± 0.03	0.12 ± 0.01

weight tends to remain proportional to body weight when the depression of body weight is due mainly to decreased feed intake. Again the three O_2 enriched groups have proportionally higher lung weights, both wet and dry, but now the helium group is clearly the least affected. In fact, lung weight of the He group, while higher, does not appear to differ significantly from either of the controls, whereas it is decidedly lower than either of the other two O_2 groups. The % weight increase of the lungs of the 100% O_2 and the 74% O_2-26% N_2 groups over that of the restricted controls is now greater than at 10 days, indicating a further exaggeration of the lung damage by these treatments. The lung weight increment still seems to be due primarily to tissue proliferation, since in comparison to controls the dry weight changes are now even more pronounced than the wet weights. A supplemental calculation of the % dry weight of the lungs was practically the same for all five groups in each time period, further showing that the O_2 effect results from an increase of tissue similar in moisture content to that of normal lung components.

Several observations in this study appear worthy of comment. First, it is evident from the increased lung weight/body weight ratios that ambient P_{O_2} in the 555-570 torr range does have an deleterious effect on the lungs. Secondly, and perhaps surprisingly, the O_2 effect is essentially one of tissue proliferation, as indicated by the fact that the dry weight increases are equal to or greater than the wet weight changes, and % dry matter remains the same. One would have speculated perhaps from past observations that edema might have been the first and most marked effect of O_2 toxicity. Thirdly, it would appear that by 20 days at least, the effect of the nonlethal hyperoxia on the lungs has been altered by the inert gas diluent present, being clearly less severe in the He group.

An explanation for the apparent helium inhibition of O_2 pulmonary toxicity is not immediately evident. On a purely physical basis, the O_2-He mixture is less dense than either 100% O_2 or O_2-N_2 and theoretically this might reduce the work of breathing, particularly in a damaged pulmonary system. Another possibility is that O_2 diffusion through the pulmonary membrane may be enhanced by He, in perhaps the same manner that O_2 uptake in some biological systems appears to be increased in the presence of helium This too should decrease the work of breathing. Both of these views, however, would require the somewhat unlikely situation that the increased lung tissue proliferation is in response to increased work of breathing in a damaged lung. The more direct view would be that hyperoxia directly stimulated tissue proliferation, possibly in the form of capillary hyperplasia, which was in turn inhibited by helium through some as yet unclear mechanism.

The improved lung picture in the He rats also appears to be associated with a slightly better body weight than in either the 100% O_2 or O_2-N_2. However, the effect on body weight is relatively small compared to that on the lungs (e.g., He body weight is only 8% higher than in O_2-N_2), whereas lung dry weight/body weight is 37% less. Other studies

have shown that the effect of hyperoxia on food intake and body weight may be distinct from its lethal and pulmonary effects.

Regardless of the mechanisms, the possibility that helium may have some moderating effect on pulmonary oxygen toxicity should be of sufficient practical importance to warrant further pursuit of this problem. It may be added that wet and dry heart, liver and kidney weights, including liver lipid, were also examined for all groups of rats and found to be relatively unaffected by the O_2 or inert gas treatment. Thus the effect on the lungs is a fairly specific response to both O_2 and He.

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